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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,311	10/31/2003	James McSwiggen	MBHB04-372 (400/137)	9826

20306 7590 02/08/2007

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EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/698,311	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,16,17,21,23,24,30,33 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,16,17,21,23,24,30,33 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/18/06 has been entered.

Status of the Application/Amendments

Applicant's response filed 12/18/06 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 6/28/06 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 12/18/06, claims 3, 16, 17, 21, 23, 24, 30, 33, and 37 are pending in the application and currently under examination.

Information Disclosure Statement

The IDS filed 12/18/06 has been entered into the application and the abstract cited therein considered.

Priority

Prior to the amendment of 12/18/06, Applicants' priority date for the currently claimed invention, Claims 3, 16, 17, 21, 23, 24, 30, 33, and 37, was considered to be that of provisional application 60/363,124, March 11, 2002.

However, with the amendment of 12/18/06, the Examiner is unable to find clear antecedent support for the newly added limitation, wherein "each purine nucleotide present in the first strand or second strand, or both the first strand and second strand of the siRNA molecule, is a 2'-O-methyl or 2'-deoxy purine nucleotide." For example, pages 10-12 of 60/363,124 do not appear to explicitly or implicitly define a single embodiment wherein each purine in the sense and/or antisense strand is modified with a 2'-O-methyl or 2'-deoxy. Support for this embodiment does appear to exist in the instant application at pages 38–42.

With regard to the amendment, Applicants have not pointed to support in any of the prior-filed application to which benefit is now claimed (MPEP 2163.06, Section I). Due to the large number and lengthy disclosures of the prior-filed applications to which benefit is now claimed, upon review, the Examiner is unable to readily find support for the instant amendments to the claims in any of the prior filed applications.

Accordingly, with the amendment of 12/18/06, the earliest effective filing date for the instantly claimed invention is considered to be that of the instant application: 10/31/03

Double Patenting—maintained

Claims 3, 16, 17, 21, 23, 24, 30, 33, and 37, as amended on 12/18/06, stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being

unpatentable over claims 1, 3, 13-21, 30, and 31 of copending Application No. 10/861,060, as amended on 10/13/06.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they claim the same or similar subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

An updated review of copending Application No. 10/861,060, shows that the application, as amended on 10/13/06, continues to claim a chemically modified, double-stranded short (18 to about 27 nucleotides) nucleic acid molecule that is complementary to a human SNCA nucleotide sequence. Also claimed are nucleic acid molecules thereof having 2'-deoxy, 2'-fluoro modified sugars, phosphorothioate linkages, and terminal cap moieties, identical to those recited in the instant application.

Accordingly, one of ordinary skill in the art would immediately recognize that the invention now claimed in the instant application (10/698,311) is obvious over the invention claimed in copending application 10/861,060.

Applicants' reply:

The reply of 12/18/06 reiterates that Applicants will consider submitting a terminal disclaimer upon indication of allowable claims.

No claims are allowable at this time.

Double Patenting—new

Claims 3, 16, 17, 21, 23, 24, 30, 33, and 37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1–35 of copending Application No. 10/562,561 in view of Ueda et al. (1993) *Proc. Natl. Acad. Sci.* 90:11282–11286 (of record).

Copending Application No. 10/562,561 claims a chemically synthesized double stranded short interfering nucleic acid (siNA) molecule that directs cleavage of an amyloid precursor protein (APP) RNA via RNA interference (RNAi), wherein each strand of said molecule is about 18 to about 23 nucleotides and one strand comprises a nucleotide sequence complementary to said APP. Also claimed are nucleic acid molecules thereof having 2'-deoxy, 2'-fluoro modified sugars, phosphorothioate linkages, and terminal cap moieties, identical to those recited in the instant application.

Ueda et al. (1993) teach the nucleotide sequence of the cDNA encoding human (alpha)-synuclein (SNCA), also known as PARK1, a 140-amino acid protein, identified as a precursor protein of the non-Aβ amyloid component (NAC). NAC is said to be an intrinsic component of amyloid plaques, proteinaceous inclusions found in patients with Alzheimer's Disease. Ueda et al. suggest on page 11286 that, "...NAC might be a factor to promote the process of amyloid formation by serving as a seed or core."

The cDNA sequence described by Ueda et al. is 100% identical to instantly recited SEQ ID NO:311, as shown by the sequence alignment below ("Result 6"). Accordingly, one of skill would have been motivated to make and use the siNA molecules disclosed in 10/562,561 to target the mRNA sequence disclosed by Ueda et al.

Accordingly, the instant claims are *prima facie* obvious over claims 1-35 of Copending Application No. 10/562,561 in view of Ueda et al.

Due to the extensive list of prior filed applications and the lengthy disclosures thereof, the Examiner is unable to readily determine whether Copending Application No. 10/562,561 is a later or earlier filed application.

This is a provisional obviousness-type double patenting rejection.

```
RESULT 6
HUMAMY
LOCUS       HUMAMY                  1549 bp    mRNA    linear   PRI 26-JAN-1994
DEFINITION  Human AD amyloid mRNA, complete cds.
ACCESSION   L08850
VERSION     L08850.1  GI:437364
KEYWORDS    AD amyloid; Alzheimer's disease; NACP; amyloid.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini;
            Hominidae; Homo.
REFERENCE   1  (bases 1 to 1549)
  AUTHORS   Ueda,K., Fukushima,H., Masliah,E., Xia,Y., Iwai,A., Yoshimoto,M.,
            Otero,D.A., Kondo,J., Ihara,Y. and Saitoh,T.
  TITLE     Molecular cloning of cDNA encoding an unrecognized component of
            amyloid in Alzheimer disease
  JOURNAL   Proc. Natl. Acad. Sci. U.S.A. 90 (23), 11282-11286 (1993)
   PUBMED   8248242
COMMENT     Original source text: Homo sapiens cDNA to mRNA.
FEATURES             Location/Qualifiers
     source          1. .1549
                     /organism="Homo sapiens"
                     /mol_type="mRNA"
                     /db_xref="taxon:9606"
                     /tissue_lib="ATCC 37432 of A. Lazzarini"
     terminator      35. .473
     CDS             53. .475
                     /standard_name="NACP"
                     /codon_start=1
                     /product="AD amyloid"
                     /protein_id="AAA16117.1"
                     /db_xref="GI:437365"
                     /translation="MDVFMKGLSKAKEGVVAAAEKTKQGVAEAAGKTKEGVLYVGSKT
                     KEGVVHGVATVAEKTKEQVTNVGGAVVTGVTAVAQKTVEGAGSIAAATGFVKKDQLGK
                     NEEGAPQEGILEDMPVDPDNEAYEMPSEEGYQDYEPEA"
     polyA_signal    1023. .1028
     polyA_site      1023
     polyA_signal    1079. .1084
     polyA_signal    1529. .1534
     polyA_site      1549
```

ORIGIN

Query Match 100.0%; Score 1543; DB 5; Length 1549;
Best Local Similarity 100.0%; Pred. No. 0;
Matches 1543; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 GGAGTGGCCATTCGACGACAGTGTGGTGTAAAGGAATTCATTAGCCATGGATGTATTCAT 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          7 GGAGTGGCCATTCGACGACAGTGTGGTGTAAAGGAATTCATTAGCCATGGATGTATTCAT 66

Qy         61 GAAAGGACTTTCAAAGGCCAAGGAGGGAGTTGTGGCTGCTGCTGAGAAAACCAAACAGGG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         67 GAAAGGACTTTCAAAGGCCAAGGAGGGAGTTGTGGCTGCTGCTGAGAAAACCAAACAGGG 126

Qy        121 TGTGGCAGAAGCAGCAGGAAAGACAAAAGAGGGTGTTCTCTATGTAGGCTCCAAAACCAA 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        127 TGTGGCAGAAGCAGCAGGAAAGACAAAAGAGGGTGTTCTCTATGTAGGCTCCAAAACCAA 186

Qy        181 GGAGGGAGTGGTGCATGGTGTGGCAACAGTGGCTGAGAAGACCAAAGAGCAAGTGACAAA 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        187 GGAGGGAGTGGTGCATGGTGTGGCAACAGTGGCTGAGAAGACCAAAGAGCAAGTGACAAA 246

Qy        241 TGTTGGAGGAGCAGTGGTGACGGGTGTGACAGCAGTAGCCCAGAAGACAGTGGAGGGAGC 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        247 TGTTGGAGGAGCAGTGGTGACGGGTGTGACAGCAGTAGCCCAGAAGACAGTGGAGGGAGC 306

Qy        301 AGGGAGCATTGCAGCAGCCACTGGCTTTGTCAAAAAGGACCAGTTGGGCAAGAATGAAGA 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        307 AGGGAGCATTGCAGCAGCCACTGGCTTTGTCAAAAAGGACCAGTTGGGCAAGAATGAAGA 366

Qy        361 AGGAGCCCCACAGGAAGGAATTCTGGAAGATATGCCTGTGGATCCTGACAATGAGGCTTA 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        367 AGGAGCCCCACAGGAAGGAATTCTGGAAGATATGCCTGTGGATCCTGACAATGAGGCTTA 426

Qy        421 TGAAATGCCTTCTGAGGAAGGGTATCAAGACTACGAACCTGAAGCCTAAGAAATATCTTT 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        427 TGAAATGCCTTCTGAGGAAGGGTATCAAGACTACGAACCTGAAGCCTAAGAAATATCTTT 486

Qy        481 GCTCCCAGTTTCTTGAGATCTGCTGACAGATGTTCCATCCTGTACAAGTGCTCAGTTCCA 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        487 GCTCCCAGTTTCTTGAGATCTGCTGACAGATGTTCCATCCTGTACAAGTGCTCAGTTCCA 546

Qy        541 ATGTGCCCAGTCATGACATTTCTCAAAGTTTTTACAGTGTATCTCGAAGTCTTCCATCAG 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        547 ATGTGCCCAGTCATGACATTTCTCAAAGTTTTTACAGTGTATCTCGAAGTCTTCCATCAG 606

Qy        601 CAGTGATTGAAGTATCTGTACCTGCCCCCACTCAGCATTTCGGTGCTTCCCTTTCACTGA 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        607 CAGTGATTGAAGTATCTGTACCTGCCCCCACTCAGCATTTCGGTGCTTCCCTTTCACTGA 666

Qy        661 AGTGAATACATGGTAGCAGGGTCTTTGTGTGCTGTGGATTTTGTGGCTTCAATCTACGAT 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        667 AGTGAATACATGGTAGCAGGGTCTTTGTGTGCTGTGGATTTTGTGGCTTCAATCTACGAT 726

Qy        721 GTTAAAACAAATTAAAAACACCTAAGTGACTACCACTTATTTCTAAATCCTCACTATTTT 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        727 GTTAAAACAAATTAAAAACACCTAAGTGACTACCACTTATTTCTAAATCCTCACTATTTT 786

Qy        781 TTTGTTGCTGTTGTTCAGAAGTTGTTAGTGATTTGCTATCATATATTATAAGATTTTTAG 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db        787 TTTGTTGCTGTTGTTCAGAAGTTGTTAGTGATTTGCTATCATATATTATAAGATTTTTAG 846

Qy        841 GTGTCTTTTAATGATACTGTCTAAGAATAATGACGTATTGTGAAATTTGTTAATATATAT 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        847 GTGTCTTTTAATGATACTGTCTAAGAATAATGACGTATTGTGAAATTTGTTAATATATAT 906

Qy        901 AATACTTAAAAATATGTGAGCATGAAACTATGCACCTATAAATACTAAATATGAAATTTT 960
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        907 AATACTTAAAAATATGTGAGCATGAAACTATGCACCTATAAATACTAAATATGAAATTTT 966

Qy        961 ACCATTTTGCGATGTGTTTTATTCACTTGTGTTTGTATATAAATGGTGAGAATTAAAATA 1020
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        967 ACCATTTTGCGATGTGTTTTATTCACTTGTGTTTGTATATAAATGGTGAGAATTAAAATA 1026

Qy       1021 AAACGTTATCTCATTGCAAAAATATTTTATTTTTATCCCATCTCACTTTAATAATAAAAA 1080
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1027 AAACGTTATCTCATTGCAAAAATATTTTATTTTTATCCCATCTCACTTTAATAATAAAAA 1086

Qy       1081 TCATGCTTATAAGCAACATGAATTAAGAACTGACACAAAGGACAAAAATATAAAGTTATT 1140
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1087 TCATGCTTATAAGCAACATGAATTAAGAACTGACACAAAGGACAAAAATATAAAGTTATT 1146

Qy       1141 AATAGCCATTTGAAGAAGGAGGAATTTTAGAAGAGGTAGAGAAAATGGAACATTAACCCT 1200
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1147 AATAGCCATTTGAAGAAGGAGGAATTTTAGAAGAGGTAGAGAAAATGGAACATTAACCCT 1206

Qy       1201 ACACTCGGAATTCCCTGAAGCAACACTGCCAGAAGTGTGTTTTGGTATGCACTGGTTCCT 1260
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1207 ACACTCGGAATTCCCTGAAGCAACACTGCCAGAAGTGTGTTTTGGTATGCACTGGTTCCT 1266

Qy       1261 TAAGTGGCTGTGATTAATTATTGAAAGTGGGGTGTTGAAGACCCCAACTACTATTGTAGA 1320
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1267 TAAGTGGCTGTGATTAATTATTGAAAGTGGGGTGTTGAAGACCCCAACTACTATTGTAGA 1326

Qy       1321 GTGGTCTATTTCTCCCTTCAATCCTGTCAATGTTTGCTTTATGTATTTTGGGGAACTGTT 1380
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1327 GTGGTCTATTTCTCCCTTCAATCCTGTCAATGTTTGCTTTATGTATTTTGGGGAACTGTT 1386

Qy       1381 GTTTGATGTGTATGTGTTTATAATTGTTATACATTTTTAATTGAGCCTTTTATTAACATA 1440
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1387 GTTTGATGTGTATGTGTTTATAATTGTTATACATTTTTAATTGAGCCTTTTATTAACATA 1446

Qy       1441 TATTGTTATTTTTGTCTCGAAATAATTTTTTAGTTAAAATCTATTTTGTCTGATATTGGT 1500
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1447 TATTGTTATTTTTGTCTCGAAATAATTTTTTAGTTAAAATCTATTTTGTCTGATATTGGT 1506

Qy       1501 GTGAATGCTGTACCTTTCTGACAATAAATAATATTCGACCATG 1543
              |||||||||||||||||||||||||||||||||||||||||||
Db       1507 GTGAATGCTGTACCTTTCTGACAATAAATAATATTCGACCATG 1549
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Claims 3, 16, 17, 21, 23, 24, 30, 33, and 37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 13–21, 30, 31, and 36 of copending Application No. 10/877,889 in view of Ueda et al. (1993) *Proc. Natl. Acad. Sci.* 90:11282–11286.

Copending Application No. 10/877,889 claims a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a distinct sense strand and a separate antisense strand, wherein each strand of said double stranded nucleic acid siNA molecule is about 18 to about 27 nucleotides in length, and comprises a nucleotide sequence complementary to an amyloid precursor protein (APP) nucleotide. Also claimed are nucleic acid molecules thereof having 2'-deoxy, 2'-fluoro modified sugars, phosphorothioate linkages, and terminal cap moieties, identical to those recited in the instant application.

Ueda et al. (1993) teach the nucleotide sequence of the cDNA encoding human (alpha)-synuclein (SNCA), also known as PARK1, a 140-amino acid protein, identified as a precursor protein of the non-Aβ amyloid component (NAC). NAC is said to be an intrinsic component of amyloid plaques, proteinaceous inclusions found in patients with Alzheimer's Disease. Ueda et al. suggest on page 11286 that, "...NAC might be a factor to promote the process of amyloid formation by serving as a seed or core."

The cDNA sequence described by Ueda et al. is 100% identical to instantly recited SEQ ID NO:311, as shown by the sequence alignment below. Accordingly, one of skill would have been motivated to make and use the siNA molecules disclosed in 10/562561 to target the mRNA sequence disclosed by Ueda et al.

Absent evidence to the contrary, an siNA molecule designed according the invention claimed in copending application 10/877,889 for RNAi mediated cleavage of the mRNA disclosed by Ueda et al. would be complementary to the amyloid precursor protein sequence now recited in application 10/877,889.

Accordingly, the instant claims are *prima facie* obvious over claims 1, 3, 13–21, 30, 31, and 36 of Copending Application No. 10/877,889 in view of Ueda et al.

Due to the extensive list of prior filed applications and the length disclosures thereof, the Examiner is unable to readily determine whether Copending Application No. 10/877,889 is a later or earlier filed application.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 17 recites the limitation "The siNA" in line 1. There is insufficient antecedent basis for this limitation in the claim. Changing "siNA" to "siRNA" would overcome this rejection.

***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 33 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Claim 33 is drawn to a pharmaceutical composition comprising the siRNA of claim 37.

The "pharmaceutical composition" language in combination with the disclosure at page 81, for example, teaching that the instantly claimed interfering nucleic acids may be used to treat and/or prevent a neurodegenerative process or condition in a subject, comprising administering to the subject a siNA molecule of the invention, requires that this claim be evaluated to determine whether the specification teaches how to use the claimed composition for treating and preventing such processes in any subject, including humans.

Problems related to the pharmaceutical use of nucleic acids were well known in the art at the time of invention. Such problems include the inability to routinely deliver an effective concentration of a specific nucleic acid into a target cell, such that a target gene is inhibited to a degree necessary to produce a therapeutic effect.

Jen et al. (2000) *Stem Cells* 18:307-319 teach that

> "One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive." (page 313, second column, second paragraph):

Hannon and Rossi (2004) *Nature* 431:371–378 teach that, while RNAi has the potential to be exploited therapeutically, and despite early proofs of principle, "there are important issues and concerns about the therapeutic application of this technology, including difficulties with delivery and uncertainty about potential toxicity." (page 374, 2nd column) "Two key challenges in developing RNAi as a therapy are avoiding off-target effects and ensuring efficient delivery." (page 377, 1st column) "The issue of delivery has restricted the antisense field for almost two

decades. It is feasible to infuse backbone-modified oligonucleotides *in vivo*, but achieving intracellular delivery at therapeutically effective concentrations is a major challenge. Targeted delivery to specific cell or tissue types is still not a practical reality for oligonucleotide-based therapeutics." (page 377, 2nd column) "As with HIV therapeutics, delivery of the siRNAs or shRNA vectors is the main challenge for successful treatment of HCV. The method of delivery used in several *in vivo* studies—hydrodynamic intravenous injection—is not feasible for the treatment of human hepatitis." (page 376) "However, enhancing siRNA stability is not enough unless the siRNAs can penetrate cells and tissue *in vivo* in concentrations sufficient to be therapeutically functional. As siRNAs are double-stranded molecules, delivery and cellular uptake is more of a challenge than for single-stranded antisense agents, which bind to serum proteins and are taken up by cells and tissues *in vivo*. There are a few reports of functional RNAi being obtained by systemic delivery of liposome-encapsulated siRNAs,..." (page 376) "Systemic delivery of siRNAs to T lymphocytes is probably not feasible owing to the immense number of these cells. Using viral vectors to deliver anti-HIV-encoding shRNA genes is also problematic, and systemic delivery is not yet practicable because the immunogenicity of the vectors themselves precludes performing multiple injections." (page 375)

Thus, the post-filing art indicates that the art of in vivo delivery of double stranded interfering nucleic acids for selectively inhibiting gene expression in animals and humans is unpredictable.

In view of the express teachings of the post-filing art suggesting that in vivo delivery of siRNA is unpredictable, it is essential that the instant application provide enabling disclosure showing how to use the invention in any and all animals. A review of the instant application fails

to find adequate representations or guidance exemplifying the use *in vivo* of the pharmaceutical preparations currently claimed. Although, applicants clearly discuss possible routes of delivery and methods of administration of nucleic acids, these teachings are general in nature, and do not teach the ordinary artisan how to effectively deliver siRNA or any other double-stranded nucleic acids, or combinations thereof to any target tissues and cells *in vivo* so as to effectively reduce gene expression of any SNCA gene to effectively treat and/or prevent a neurological disorder in any subject.

Thus, the amount of disclosure is insufficient given the level of unpredictability in the art. For example, the instant application does not appear to teach one of skill in the art how to effectively target tissues and cells in the brain. Similarly, while the instant application is enabling for the use of double stranded nucleic acids to transfect cells in culture, it does not enable the use of these molecules *in vivo* in a way that would reasonable enable one of skill in the art to use the invention so as to obtain a desired result, e.g., phenotype or outcome in an individual.

A review of the instant application finds a number of working and prophetic examples (pp.132–140); however, these examples are directed to the cellular uptake and inhibition of SNCA (PARK) by siRNAs *in vitro* (in cell culture), and the one example directed to an animal model is prophetic in nature and does not adequately represent the delivery of siRNA to animals and humans for the treatment or prevention of diseasese. Therefore, the examples do not teach one of skill how to deliver these siRNAs into cells *in vivo* to treat any particular condition. That is, no technical guidance or exemplary disclosure is provided regarding the use of the claimed pharmaceutical compositions for targeting genes in cells and tissues in living organisms, including any mammal.

As the post-filing art indicates, in culture results are not readily extrapolated to *in vivo* applications.

Given this unpredictability, the skilled artisan would require specific guidance to practice use the claimed pharmaceutical compositions to treat one or more disorders *in vivo* in any given patient. That is, specific guidance would be required to teach one of skill in the art how to use the claimed compositions to produce a positive effect in a patient.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The teachings of the prior art does not provide that guidance, such that the skilled artisan would be able to use the claimed pharmaceutical compositions in the manner disclosed to produce the intended effects of treating the disclosed diseases.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement. Removing the "pharmaceutical" language from the instant claim would overcome this rejection.

Claim Rejections - 35 USC § 103

Claims 3, 16, 17, 21, 23, 24, 30, 33, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masliah (WO 95/06407); Tuschl et al. (US 2004/0259247); Bass (2001) *Nature* 411:428-9; Parrish et al. (2000) *Molecular Cell* 6:1077-1087; Usman et al. (2000) *J. Clin. Investigation* 106:1197–1202; Beigelman et al. (1995) *Nucleic Acids Res.* 23:4434–4442; Cook et al. (U.S. Patent 6,005,087); Matulic-Adamic (U.S. Patent 5,998,203); and Ortigao et al. (1992) *Antisense Res. Dev.* 2:129-146.

Independent claim 37, as amended on 12/18/06, is described above.

Masliah teaches the cDNA sequence, properties, and biological functions of the 140 amino acid amyloid precursor protein (NACP), found in amyloid deposits in Alzheimer's disease patients. In particular, Masliah teaches SEQ ID NO:1 (Fig. 2 and see sequence listing), found by the Office to comprise instantly recited SEQ ID NO:311 in its entirety (see alignment "Result 2" below), and its correlation to Alzheimer's disease.

NACP is said by Masliah to be a highly abundant synaptic protein, which degrades to form NAC. Self-aggregating, NAC is said to have a significant ability to bind to itself and become part of amyloid fibrils and neuritic plaques observed in the brains of patients afflicted with Alzheimer's disease. Masliah teaches a correlation between abnormal processing and accumulation of amyloid precursor proteins and the neurological degeneration characteristic of Alzheimer's disease (see pp. 1-8, for example), stating for example, that the cognitive dysfunction that characterizes AD is apparently attributable to synaptic loss. Recent studies

strongly suggests that there is a connection between the abnormal processing of synaptic proteins and amyloid formation (page 4).

Masliah further suggests using antisense oligonucleotides and ribozymes targeted to NACP (SEQ ID NO:1) to inhibit or reduce the build up of amyloid deposits (see pages 26-27, 35-36, and 49-56). For example, Masliah states that The NAC polynucleotide in the form of an antisense polynucleotide is useful in treating disease states associated with formation of amyloid i.e., amyloidosis in the brain, (particularly in neuritic) plaques by preventing expression of the protein that is originating. Essentially, any disorder which is etiologically linked to expression of NACP could be considered susceptible to treatment with a reagent of the invention which modulates NACP expression. Masliah goes on to state that when amyloidosis is associated with NACP overexpression, such suppressive reagents as an antisense NACP polynucleotide sequence can be introduced into a cell (page 35-36). At page 51, Masliah teaches that antisense nucleic acids are DNA or RNA molecules that are complementary to at least a portion of a specific mRNA molecule, that antisense nucleic acids hybridize to the corresponding mRNA, forming a double-stranded molecule, and that antisense nucleic acids interfere with the translation of the mRNA since the cell will not translate a mRNA that is double-stranded. Antisense oligomers of about 15 nucleotides are preferred. It is said that the use of antisense methods to inhibit the in vitro translation of genes is well known in the art.

Accordingly, Masliah teaches methods and materials for making and using antisense oligonucleotides and ribozymes complementary to a sequence comprising instantly recited SEQ ID NO:311 to inhibit the expression of an amyloid precursor protein and thereby treat diseases associated with amyloid deposition .

Masliah does not teach or suggest making or using chemically modified siRNAs directed to amyloid precursor protein.

Tuschl et al. (US 2004/0259247) teaches methods and materials for making and using double stranded, short (19-23 nt) interfering RNA against virtually any known gene as tools to investigate gene function and/or treat disease (paragraphs 1-33, for example). It is taught that the ribonucleotide duplexes may comprise one or more chemical modifications in either the sense or antisense strand (paragraphs 15 and 16). Preferred modifications are said to be backbone and sugar modifications. Exemplary sugar-modified ribonucleotides include those in which the 2'-OH group is replaced by H, halo, or OR group, where R is any C1-C6 alkyl and halo is any halogen, such as fluorine. Exemplary backbone modifications include those in which the phosphoester group is replaced by a phosphorothioated group. Importantly, Tuschl et al. expressly state that "The above modifications may be combined." (paragraph 16, bottom) This is interpreted to mean that one or more ribonucleotide units in either the sense or antisense strands, or in both strands, may be modified one or more 2' positions and at one or more internucleoside linkages.

At paragraph 166, Tuschl et al. teach that while 8 out of 42 nt of a siRNA duplex were replaced by DNA residues without loss of activity, complete substitution of one or both siRNA strands by 2'-deoxy or 2/-O-methyl residues abolished RNAi.

Tuschl et al. also teach pharmaceutical compositions comprising siRNA (paragraphs 32 and 33).

Accordingly, Tuschl et al. teach and suggest methods and materials for making and using chemically modified siRNAs against virtually any known gene and/or therapeutic target. Tuschl

et al. teach both explicitly and implicitly that chemical modification is a result-effective variable influencing both the activity and nuclease stability of an siRNA molecule.

Importantly, Tuschl et al. also compare siRNA methodology to that of antisense and ribozyme techniques for inhibiting gene expression. At paragraph 148, for example, Tuschl et al. state that siRNAs are extraordinarily powerful reagents for mediating gene silencing and that siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments. At paragraph 137, Tusch et al. state that the remarkable finding that synthetic 21 and 22 nt siRNA duplexes can be used for efficient mRNA degradation provides new tools for sequence-specific regulation of gene expression in functional genomics as well as biomedical studies. The siRNAs may be effective in mammalian systems where long dsRNAs cannot be used due to the activation of the PKR response. As such, the siRNA duplexes represent a new alternative to antisense or ribozyme therapeutics.

Bass teaches that, like some antisense oligonucleotides, which trigger RNase H-catalyzed cleavage of their targets, siRNAs trigger the degradation of complementary messenger RNAs (page 428 and Fig. 1). A general outline of the RNAi mechanism is taught, showing how siRNA-mediated RNAi may be used to interfere with gene expression using siRNAs directed against specific mRNA sequences (Fig. 1). Bass teaches that RNAi has repeatedly proven itself to be more robust that antisense techniques: it works more often, and typically decreases expression of a gene to lower levels, or eliminates it entirely. Furthermore, siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments.

The prior art teaches, then, that siRNAs, antisense oligonucleotides, and ribozymes can be used to produce the same effect, albeit with different potencies and by different biochemical mechanisms. siRNAs, antisense oligos, and ribozymes can both be used to inhibit gene expression *in vivo* or *in vitro*, via mRNA degradation or translation attenuation, and, thus, both types of nucleic acids may be used to prevent the expression of a gene in a cell. For example, Bass teaches that antisense RNA is another technique to prevent the expression of particular genes (page 429). Thus, in this sense, siRNAs, antisense oligos, and ribozymes are art-recognized equivalents that may be used for the same purpose: reducing or inhibiting gene expression. (See for example MPEP §2144.06, SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE.)

Nevertheless, as explained above, siRNAs possess certain advantages over antisense oligos and ribozymes which would motivate one of ordinary skill in the art to select siRNAs over antisense oligos to more efficiently block and/or reduce the expression of any given target gene, particularly a gene known to be involved in a neurodegenerative disease such as Alzheimer's.

One of skill would have been further motivated to make and use chemically modified siRNAs for sequence specific inhibition of amyloid precursor protein, given that the prior art teaches and suggests using chemical modification to prevent nuclease-catalyzed degradation of RNA and DNA-based drugs in cells and tissues in vitro and in vivo.

The prior art is replete with reports teaching and suggesting materials and methods for chemically modifying ribozymes, antisense oligonucleotides, short and long double-stranded interfering RNAs as a means to increase nuclease resistance and enhance inhibitory activity. One of skill in the antisense, ribozyme, and RNAi arts would be commended to the teachings in each

of these fields for information and technical guidance regarding the types of modifications that may be incorporated into RNA and DNA-based oligonucleotides without adversely affecting hybridization properties and biological activity.

For example, as stated above, Tuschl et al. teach that siRNAs may be modified without loss of activity, but that full modification of the sense or antisense strand depletes activity.

Parrish et al. teach that many modifications, including 2'-fluoro, 2'-deoxy, and phosphorothioates, at A, C, or G residues are compatible with full interference activity (page 1081). Parrish et al. teach that RNAi activity is more sensitive to modification of the antisense strand than the sense strand, and that the affect of a dsRNA depends on the type and extent of modification employed (page 1081). Accordingly, Parrish et al. echo Tuschl et al., showing that while siRNAs tolerate some types of modifications along the sugar-phosphate backbone at purine and/or pyrimidine residues, chemical modification is a result-effective variable, requiring optimization (MPEP 2144.05).

Usman et al. teach that due to the abundance of ribonucleases in cellular fluids and tissues, it is important to protect ribozymes against nuclease degradation (page 1197). Usman teaches that several modifications have been developed, including 2'-O-methyl modifications, inverted deoxyabasic modifications to provide a 3'-3' linkage at the 4' terminus, and the addition of three or four phosphorothioate linkages at the 5' end. Usman suggests limiting the number of phosphorothioates to reduce non-specific hybridization in the cell. Usman et al. suggest combining these modifications for improved biological stability but caution against modifying the catalytic core purine residues (page 1198). Usman et al. teach that the optimal placement,

combination, and type of modification useful for generating generic, nuclease resistant ribozymes may be identified empirically (page 1197).

Beigelman et al. teach that the degradation of hammerhead ribozymes is consistent with RNase A-like endonuclease cleavage at pyrimidine containing sites (page 4438) and that extensive modification with 2'-O-methyl is tolerated (page 4438).

Cook et al. teach that a variety of chemical modifications may be introduced into the sugar-phosphate backbone of antisense oligonucleotides to enhance their resistance to endo- and exonuclease degradation and increase their overall activity (col. 1 and 2 and cols. 36-58). Modifications recommended include 2'-fluoro, 2'-O-methyl, and phosphorothioates (col. 6). Cook et al. teach that antisense activity varies with the placement, type, and extent of modification introduced (cols. 36-58).

Matulic-Adamic et al. teach double stranded nucleic acids comprising inverted abasic terminal cap moieties that provide resistance to degradation (see column 2, lines 44-55; column 3 lines 1-68; columns 8-9; and Fig. 13). Matulic-Adamic et al. further teach a double stranded structure comprising separate sense and antisense strands and further wherein this structure comprises a connecting loop comprising a linker or non-nucleotide linker (see Figure 3).

Ortigao et al. teach the addition of 3'-3'-linked and 5'-5'-linked inverted deoxyribonucleotide residues, including inverted deoxythymidine (iT) residues, at the 3'- and 5' ends of DNA antisense oligonucleotides to enhance their resistance to exononuclease-catalyzed degradation. It is shown that the introduction of end-inverted nucleotides does not have any noticeable influence on duplex formation and that end inverted antisense oligos are able to inhibit gene expression *in vitro* and *in vivo* in a concentration dependent manner. Furthermore, it

is shown that end inversion increases the half-life of an antisense oligo in human serum from 20 min to 30 h. It is further shown that the introduction of end-inverted linkages is compatible with standard methods of DNA synthesis.

It is clear from the prior art, then, that chemical modification is a result-effective variable, requiring optimization. It is further clear from the prior art that a wide variety of 2'-sugar and phosphate backbone modifications, including those now claimed, may be incorporated into RNA based drugs singly or in combination with beneficial results and without adverse affects. The prior art is specific with regard to the type, extent, and placement of modifications in antisense, ribozyme, and siRNA nucleic acids, which share a common utility and have similar chemistries.

Accordingly, it would have been obvious at the time the instant invention was made to make and use chemically modified siRNAs as now claimed, complementary to and capable of inhibiting the expression of a human amyloid precursor protein sequence comprising instant SEQ ID NO:311 to treat a disorder such as Alzheimer's associated with amyloid plaque deposition.

One of skill would have been well motivated and have had a reasonable expectation of success given that the combination of cited prior art references as a whole teach the materials and methods for making and using chemically modified siRNAs for RNAi-mediated inhibition, suggest that chemical modification may be used effectively to significantly enhance the activity and nuclease stability of RNA and DNA-based drugs, and show that siRNAs are a superior alternative to both antisense and ribozyme oligonucleotides. In view of these combined teachings, it would have been obvious to substitute the chemically modified, nuclease resistant siRNAs taught by the prior art for the antisense oligonucleotides suggested by Masliah for use

against the amyloid precursor protein (NACP), to more effectively inhibit amyloid deposition in the brains of Alzheimer's patients and/or study the role of NACP in neuronal cell lines in culture.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Response to Arguments

In response to the previous rejection of the claims (Office Action of 6/28/06), Applicants argue at pages 6-9 of their Remarks that Tuschl et al. teach away from the instantly claimed invention in that Tuschl teaches away from the extensive use of 2'-O-methyl or 2'-deoxy modifications.

Applicants argue that Tuschl is the only reference addressing chemically modified siRNAs having "extensive modification with 2'-deoxy (2'-H) or 2'-O-methyl" nucleotides, and demonstrates that such modified siRNAs are inactive. Accordingly, the ordinary artisan would have derived no level of assurance from any of the cited references (or any other reference known to Applicant) that similar modifications would result in active siRNA molecules.

Applicants argue that Parrish teaches only chemically modified long dsRNA constructs of greater than 720 nucleotides in length, that Matulic-Adamic teaches ribozyme technology, that Ortigao teach single stranded antisense technology, and that no reference or combination of references teach the combination of different modifications as is presently claimed, let alone a combination that involves extensive 2'-O-methyl or 2'-deoxy modification or purine nucleotides along with 2'- deoxy-2'-fluoro pyrimidine modifications.

Applicants argue in essence that the cited references provide neither a motivation nor a reasonable expectation of success for making the claimed invention.

Applicants' remarks have been fully considered but are not found persuasive.

Applicants appear to contest the rejection specifically with regard to the modification of siRNA as now claimed, with all its limitations (see claim 37).

However, the instant claims, as amended on 12/18/06, do not require "extensive" modification, only that each purine and that one or more pyrimidines be modified. The absolute number and precise arrangement of the methyl, deoxy, and fluoro modifications in the sense and antisense strands will vary, depending on the nucleotide sequence. In fact, the instant claims encompass a large genus of differentially modified siRNAs.

No evidence is found either in the instant application or the prior art showing that the instantly claimed modifications or arrangements thereof would be more or less preferable to any other modification or configuration of modifications taught by the prior art. Moreover, one of skill would have been lead to a number of species within the scope of the instantly claimed invention, given the large variety of exemplary embodiments taught in the prior art and the explicit and implicit disclosures in the prior art that many combinations thereof are possible.

The Examiner submits that ribozymes, antisense oligonucleotides, and siRNAs are art-recognized equivalents inasmuch as each belongs to the growing collection of nucleic acid based drugs used for inhibiting gene expression in cells in vitro and in vivo. They involve similar chemistries and are amenable to similar modifications for improving nuclease resistance. It was within the knowledge of one of skill in the art, and is implicitly communicated by the prior art, to make such modifications with an eye to improving nuclease resistance while being mindful of the affect on the molecule's inhibitory activity.

The Examiner submits that Tuschl et al. do not teach away from the invention now claimed. Rather Tuschl et al. teach that extensive modification with 2'-deoxy (2'-H) or 2'-O-methyl will abolish RNAi activity, but that some modification is tolerated. Accordingly, there is a balance. When read in combination with the many other prior art reports teaching chemical

modification of antisense, ribozyme, and interfering dsRNAs, one of skill would have understood that a wide variety of chemical modifications may be applied to the sugar-phosphate backbone of the sense and antisense strands of siRNAs, and that the selection and arrangement of these modifications would influence the activity and stability of the oligonucleotide. Only routine experimentation would have been required to make and use such molecules, and reasonable success would have been expected given the large number of examples in the prior art and detailed guidance regarding the general principles as to which modifications are tolerated and which ones are not.

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (MPEP 2144.05).

Obviousness does not require absolute predictability, however, at least some degree of predictability is required (MPEP 2143.02).

In the instant case, the prior art teaches both the specific and general materials, methods, and conditions for incorporating chemical modifications into RNA and DNA based nucleic acid therapeutics, including ribozymes, antisense oligonucleotides, and RNAi active siRNAs.

The combination of references clearly show that modification is a result-effective variable requiring optimization to balance nuclease stability and activity. For example, Beigelman et al. teach the optimization of nuclease resistance and cleavage activity of ribozymes through selective modification at different positions in the ribozyme. Parrish and Tuschl teach different and selective modification of interfering RNAs with deoxy and O-methyl. Cook et al. teach selective modification of antisense.

Accordingly, it is submitted that the combined references, as a whole, motivate one of skill in the art to make and use a wide variety of chemically modified siRNAs within the scope of the invention, and provide a reasonable level of success that many different embodiments within the scope of the instant invention will perform the required function.

Thus in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

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RESULT 2 (Masliah WO/9506407)
PCT-US94-09789-1
; Sequence 1, Application PC/TUS9409789
;  GENERAL INFORMATION:
;    APPLICANT:  The Regents of the University of California
;    TITLE OF INVENTION:  NOVEL COMPONENT OF AMYLOID IN
;    TITLE OF INVENTION:  ALZHEIMER'S DISEASE AND METHODS FOR USE OF SAME
;    NUMBER OF SEQUENCES:  12
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Spensley Horn Jubas & Lubitz
;      STREET:  1880 Century Park East - Suite 500
;      CITY:  Los Angeles
;      STATE:  California
;      COUNTRY:  USA
;      ZIP:  90067
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.25
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  PCT/US94/09789
;      FILING DATE:  29-AUG-1994
;      CLASSIFICATION:
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  Howells, Stacy L.
;      REGISTRATION NUMBER:  34,842
;      REFERENCE/DOCKET NUMBER:  FD-3520
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (619) 455-5100
;      TELEFAX:  (619) 455-5110
;  INFORMATION FOR SEQ ID NO:  1:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  1560 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  single
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  DNA (genomic)
;    IMMEDIATE SOURCE:
;      CLONE:  cDNA for NACP
;    FEATURE:
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;       NAME/KEY:  misc_RNA
;       LOCATION:  1..1560
PCT-US94-09789-1

  Query Match             100.0%;  Score 1543;  DB 7;  Length 1560;
  Best Local Similarity   100.0%;  Pred. No. 0;
  Matches 1543;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GGAGTGGCCATTCGACGACAGTGTGGTGTAAAGGAATTCATTAGCCATGGATGTATTCAT 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          7 GGAGTGGCCATTCGACGACAGTGTGGTGTAAAGGAATTCATTAGCCATGGATGTATTCAT 66

Qy         61 GAAAGGACTTTCAAAGGCCAAGGAGGGAGTTGTGGCTGCTGCTGAGAAAACCAAACAGGG 120
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Db         67 GAAAGGACTTTCAAAGGCCAAGGAGGGAGTTGTGGCTGCTGCTGAGAAAACCAAACAGGG 126

Qy        121 TGTGGCAGAAGCAGCAGGAAAGACAAAAGAGGGTGTTCTCTATGTAGGCTCCAAAACCAA 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        127 TGTGGCAGAAGCAGCAGGAAAGACAAAAGAGGGTGTTCTCTATGTAGGCTCCAAAACCAA 186

Qy        181 GGAGGGAGTGGTGCATGGTGTGGCAACAGTGGCTGAGAAGACCAAAGAGCAAGTGACAAA 240
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Db        187 GGAGGGAGTGGTGCATGGTGTGGCAACAGTGGCTGAGAAGACCAAAGAGCAAGTGACAAA 246

Qy        241 TGTTGGAGGAGCAGTGGTGACGGGTGTGACAGCAGTAGCCCAGAAGACAGTGGAGGGAGC 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        247 TGTTGGAGGAGCAGTGGTGACGGGTGTGACAGCAGTAGCCCAGAAGACAGTGGAGGGAGC 306

Qy        301 AGGGAGCATTGCAGCAGCCACTGGCTTTGTCAAAAAGGACCAGTTGGGCAAGAATGAAGA 360
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Db        307 AGGGAGCATTGCAGCAGCCACTGGCTTTGTCAAAAAGGACCAGTTGGGCAAGAATGAAGA 366

Qy        361 AGGAGCCCCACAGGAAGGAATTCTGGAAGATATGCCTGTGGATCCTGACAATGAGGCTTA 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        367 AGGAGCCCCACAGGAAGGAATTCTGGAAGATATGCCTGTGGATCCTGACAATGAGGCTTA 426

Qy        421 TGAAATGCCTTCTGAGGAAGGGTATCAAGACTACGAACCTGAAGCCTAAGAAATATCTTT 480
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Qy        481 GCTCCCAGTTTCTTGAGATCTGCTGACAGATGTTCCATCCTGTACAAGTGCTCAGTTCCA 540
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Db        487 GCTCCCAGTTTCTTGAGATCTGCTGACAGATGTTCCATCCTGTACAAGTGCTCAGTTCCA 546

Qy        541 ATGTGCCCAGTCATGACATTTCTCAAAGTTTTTACAGTGTATCTCGAAGTCTTCCATCAG 600
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Qy        601 CAGTGATTGAAGTATCTGTACCTGCCCCCACTCAGCATTTCGGTGCTTCCCTTTCACTGA 660
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Db        607 CAGTGATTGAAGTATCTGTACCTGCCCCCACTCAGCATTTCGGTGCTTCCCTTTCACTGA 666

Qy        661 AGTGAATACATGGTAGCAGGGTCTTTGTGTGCTGTGGATTTTGTGGCTTCAATCTACGAT 720
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Qy        721 GTTAAAACAAATTAAAAACACCTAAGTGACTACCACTTATTTCTAAATCCTCACTATTTT 780
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Db        727 GTTAAAACAAATTAAAAACACCTAAGTGACTACCACTTATTTCTAAATCCTCACTATTTT 786
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Qy        781 TTTGTTGCTGTTGTTCAGAAGTTGTTAGTGATTTGCTATCATATATTATAAGATTTTTAG 840
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Db        787 TTTGTTGCTGTTGTTCAGAAGTTGTTAGTGATTTGCTATCATATATTATAAGATTTTTAG 846

Qy        841 GTGTCTTTTAATGATACTGTCTAAGAATAATGACGTATTGTGAAATTTGTTAATATATAT 900
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Db        847 GTGTCTTTTAATGATACTGTCTAAGAATAATGACGTATTGTGAAATTTGTTAATATATAT 906

Qy        901 AATACTTAAAAATATGTGAGCATGAAACTATGCACCTATAAATACTAAATATGAAATTTT 960
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Db        907 AATACTTAAAAATATGTGAGCATGAAACTATGCACCTATAAATACTAAATATGAAATTTT 966

Qy        961 ACCATTTTGCGATGTGTTTTATTCACTTGTGTTTGTATATAAATGGTGAGAATTAAAATA 1020
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Qy       1021 AAACGTTATCTCATTGCAAAAATATTTTATTTTTATCCCATCTCACTTTAATAATAAAAA 1080
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1027 AAACGTTATCTCATTGCAAAAATATTTTATTTTTATCCCATCTCACTTTAATAATAAAAA 1086

Qy       1081 TCATGCTTATAAGCAACATGAATTAAGAACTGACACAAAGGACAAAAATATAAAGTTATT 1140
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Db       1087 TCATGCTTATAAGCAACATGAATTAAGAACTGACACAAAGGACAAAAATATAAAGTTATT 1146

Qy       1141 AATAGCCATTTGAAGAAGGAGGAATTTTAGAAGAGGTAGAGAAAATGGAACATTAACCCT 1200
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Qy       1201 ACACTCGGAATTCCCTGAAGCAACACTGCCAGAAGTGTGTTTTGGTATGCACTGGTTCCT 1260
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Db       1207 ACACTCGGAATTCCCTGAAGCAACACTGCCAGAAGTGTGTTTTGGTATGCACTGGTTCCT 1266

Qy       1261 TAAGTGGCTGTGATTAATTATTGAAAGTGGGGTGTTGAAGACCCCAACTACTATTGTAGA 1320
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Db       1267 TAAGTGGCTGTGATTAATTATTGAAAGTGGGGTGTTGAAGACCCCAACTACTATTGTAGA 1326

Qy       1321 GTGGTCTATTTCTCCCTTCAATCCTGTCAATGTTTGCTTTATGTATTTTGGGGAACTGTT 1380
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1327 GTGGTCTATTTCTCCCTTCAATCCTGTCAATGTTTGCTTTATGTATTTTGGGGAACTGTT 1386

Qy       1381 GTTTGATGTGTATGTGTTTATAATTGTTATACATTTTTAATTGAGCCTTTTATTAACATA 1440
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1387 GTTTGATGTGTATGTGTTTATAATTGTTATACATTTTTAATTGAGCCTTTTATTAACATA 1446

Qy       1441 TATTGTTATTTTTGTCTCGAAATAATTTTTTAGTTAAAATCTATTTTGTCTGATATTGGT 1500
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1447 TATTGTTATTTTTGTCTCGAAATAATTTTTTAGTTAAAATCTATTTTGTCTGATATTGGT 1506

Qy       1501 GTGAATGCTGTACCTTTCTGACAATAAATAATATTCGACCATG 1543
              |||||||||||||||||||||||||||||||||||||||||||
Db       1507 GTGAATGCTGTACCTTTCTGACAATAAATAATATTCGACCATG 1549
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Response to Applicants' Arguments

Applicants' arguments presented on 12/18/06 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and/or in view of the new and/or reiterated rejections stated herein, above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LVW
Examiner Art Unit 1635
January 30, 2007

SEAN McGARRY
PRIMARY EXAMINER
1635